Weiss, S.T., Tager, I.B., Speizer, F.E., Rosner, B. "Persistent Wheeze: Its Relation to Respiratory Illness, Cigarette Smoking, and Level of Pulmonary Function in a Population Sample of Children" American Review of Respiratory Disease 122: 697-707, 1980.

SUMMARY: In a study of early-life risk factors for the development of adult obstructive airway disease, respiratory symptoms, disease and smoking histories, and spirometry were obtained for 650 children 5 to 9 yr of age and their families in East Boston, Massachusetts. Persistent wheezing was the most frequently reported chronic symptom, occurring in 9.2% (60/650) of the population. Children with persistent wheezing were more likely to report cough and phlegm ($p<0.001$), a history of asthma ($p<0.001$), hay fever ($p<0.02$), or past hospitalization with a respiratory illness ($p<0.001$) than their asymptomatic peers. Prospective evaluation of a subsample of the 650 children confirmed a greater occurrence of acute lower respiratory illness in those children with persistent wheeze.

Parental cigarette smoking was linearly related to the occurrence of persistent wheeze ($p=0.012$) and lower degrees of mean normalized forced expiratory flow during the middle half of the forced vital capacity (FEF-Z score). A multiple linear regression identified the mother's current smoking status and current persistent wheeze as significant predictors of the children's mean FEF-Z score. Other variables, such as the father's smoking, children's personal smoking, a doctor's diagnosis of asthma, and a past history of lower respiratory illness were not significant predictors of the FEF-Z score.

Persistent Wheeze

Its Relation to Respiratory Illness, Cigarette Smoking, and Level of Pulmonary Function in a Population Sample of Children[1-3]

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SUMMARY

In a study of early-life risk factors for the development of adult obstructive airway disease, respiratory symptoms, disease and smoking histories, and spirometry were obtained for 650 children 5 to 9 yr of age and their families in East Boston, Massachusetts. Persistent wheezing was the most frequently reported chronic symptom, occurring in 9.2% (60/650) of the population. Children with persistent wheezing were more likely to report cough and phlegm ($p < 0.001$), a history of asthma ($p < 0.001$), hay fever ($p < 0.02$), or past hospitalization with a respiratory illness ($p < 0.001$) than their asymptomatic peers. Prospective evaluation of a subsample of the 650 children confirmed a greater occurrence of acute lower respiratory illness in those children with persistent wheeze.

Parental cigarette smoking was linearly related to the occurrence of persistent wheeze ($p = 0.012$) and lower degrees of mean normalized forced expiratory flow during the middle half of the forced vital capacity (FEF-Z score). A multiple linear regression identified the mother's current smoking status and current persistent wheeze as significant predictors of the children's mean FEF-Z score. Other variables, such as the father's smoking, children's personal smoking, a doctor's diagnosis of asthma, and a past history of lower respiratory illness were not significant predictors of the FEF-Z score.

Introduction

The most important risk factor for the development of chronic respiratory symptoms and airflow obstruction in adults is cigarette smoking (1). However, a small number of adults with chronic airflow obstruction have never smoked, and many lifelong smokers never develop respiratory symptoms or clinical evidence of chronic airflow obstruction. The explanation for this individual susceptibility to the effect of direct exposure to cigarettes is unknown (2). Among the factors studied to date in adult populations, e.g., α-antitrypsin polymorphism (3), atopic diathesis (4), and a retrospective history of childhood respiratory illness (5, 6), none has provided clear insights into this susceptibility.

Epidemiologic studies of respiratory disease in children have demonstrated that children with chronic respiratory symptoms have lower degrees of pulmonary function (7, 8). The hypothesis that factors such as lower respiratory illness, atopic

(*Received in original form January 2, 1980 and in revised form August 4, 1980*)

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[2] Supported by Grant No. HL21063, Contract No. LHR3-2906, and Training Grant in Clinical Epidemiology No. HL05998 from the Division of Lung Disease, National Heart, Lung and Blood Institute.

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diathesis, and cigarette smoking acting during childhood may be important in the subsequent development of chronic airflow obstruction in adult life has been suggested. As part of a prospective study of early-life risk factors for the development of chronic airflow obstruction, we determined the relation of chronic respiratory symptoms (current persistent wheeze and chronic cough and phlegm) to the occurrence of lower respiratory illness, atopic diathesis, personal and parental cigarette smoking habits, and the level of pulmonary function in a population sample of children.

Methods

Selection of sample. A random sample was taken of all children 5 to 9 yr of age (index children) in the public and parochial schools of East Boston as of September 1974 (Twenty-two children 4 yr of age and 5 children 10 yr of age were included in the sample because they appeared on the school registration lists from which the sample was actually drawn). Thirty-two per cent of all children in each school in the study community were randomly chosen to ensure a uniform geographic distribution in the study population. The number of children initially selected for study was based on estimates of expected refusal rates and on the estimated sample needed for a follow-up of familial patterns of chronic productive cough as determined from a previous study in this community (9).

East Boston is a geographically defined neighborhood within the city of Boston. Its inhabitants are of predominantly Italian-American descent. Sixty-three per cent of the working adults in the study sample were clerks (or in related positions), craftsmen, service workers, or one of the other operatives defined by the U.S. Census (10). Five per cent of them held professional, technical, or managerial positions. Approximately 40% of the adults had a high school diploma.

Screening of sample. The households of the selected children were visited between January and June 1975 by specially trained interviewers (trained using materials provided by the Division of Lung Diseases, National Heart, Lung and Blood Institute), and the persons in the households were enumerated. All members of the household were then asked to attend a special neighborhood clinic for the purpose of obtaining respiratory symptom and illness histories and measures of pulmonary function. Those families who agreed to participate but did not come to the clinic were interviewed at home. Standardized questionnaires were used to obtain histories and demographic data for all members of the household. Separate questionnaires were administered by the interviewers for subjects younger than 10 yr of age and for those older than 10. Questions relating to chronic cough, phlegm, and chest illness were those proposed by the Division of Lung Diseases, National Heart, Lung and Blood Institute (11). Mothers answered all questions for children 10 yr of age or younger except those questions pertaining to the child's smoking history. Smoking histories were obtained from children individually in the absence of their parents during the pulmonary function testing.

In addition to the respiratory symptom and retrospective illness histories obtained for all index children and their siblings at entrance into the study, the acute respiratory illness experience for the index children was assessed prospectively over a 2-yr period using methods previously described (12). Briefly, parents of the index children were contacted by telephone every 2 wk (except in July and August) for the 2-yr period from September 1975 through June 1977. Index children who experienced one or more selected respiratory symptoms in the previous 2 wk were visited in their homes, and a more detailed history of their respiratory symptoms was obtained. Definitions of upper and lower respiratory illness were identical to those proposed by Monto and associates (13), with the exception that the lower respiratory episodes characterized by wheeze as the sole criteria were not counted as lower respiratory illness.

Definitions of respiratory symptoms and illnesses. Current wheezing was assessed on the basis of the following questions posed by the interviewers:

"Does _____'s breathing ever sound wheezy or whistling?"

(*1*) No. If yes, ask: (*2*) Does this occur only with colds? (*3*) Does this occur occasionally apart from colds? (*4*) Does this occur most days or nights? (*5*) Does this occur with colds and occasionally apart from colds?

For the purpose of this report, the absence of current wheezing was defined as a response of "no" or wheezing "only with colds." Children with wheezing "occasionally apart from colds" only were excluded from the analysis. Current persistent wheezing was defined as wheezing that occurred "with colds and occasionally apart from colds" or "most days and nights."

Chronic cough and phlegm was defined as cough and sputum production for any 3 months in any 1 year.

Specific respiratory illnesses were defined in terms of parental response to each of the following questions:

"Has a doctor ever told you that your child has ever had. . . . (*1*) asthma? (*2*) hay fever? (*3*) eczema? (*4*) croup? (*5*) bronchitis? (*6*) bronchiolitis? (*7*) pneumonia?"

The age at the time of first diagnosis and the total number of episodes of each illness were also recorded.

The presence of an atopic diathesis was defined as a positive response to the questions: "Has a doctor ever told you that you had . . . (*a*) hay fever? (*b*) asthma? (*c*) eczema?" (Each asked separately.)

Definitions of cigarette smoking. A parent was defined as having never smoked if she/he never smoked, smoked less than 1 cigarette per day, or smoked less than a total of 20 packs during her/his lifetime. A current smoker was defined as one who smoked more than the above amount and was smoking within 1 month of the time of interview. Ex-smokers were defined as persons who had stopped smoking more than 1 month before the time of

the interview, and had smoked more than the above amounts previously.

Households were classified as nonsmoking if both parents were "never" smokers. Smoking households were divided into those in which both parents were "current" smokers and households in which only 1 parent was a "current" smoker and the other parent either a "never" smoker or an ex-smoker. Households in which only a single parent was interviewed were excluded from this analysis.

A child was considered to have never smoked if he or she never smoked. A child was classified as an ever-smoker if he or she had at sometime smoked a cigarette, regardless of amount, as determined by response to a series of standardized questions asked in the absence of parents.

Pulmonary function testing. Forced vital capacity (FVC) maneuvers were performed in the sitting position without a noseclip, using an 8-L, water-filled, portable recording spirometer (Survey Spirometer; Warren Collins, Inc., Braintree, MA). A tracing was considered acceptable if it was at least 4 s in duration and if the interviewer felt that a maximal effort had been made. All tests on children were done by 1 or 2 interviewers, each with at least 2 yr of experience. Standing height was measured without shoes to the nearest one half inch. Forced expiratory volume in one second (FEV_1) and forced expiratory flow during the middle half of the FVC (FEF_{25-75}) were obtained by standard techniques (14). After correcting volumes to BTPS, per cent predicted values were obtained using the nomograms of Dickman and co-workers (15).

Analysis of data. The $FEF_{25-75\%}$ was used in the present analysis because it provided better discrimination between children in the various household smoking groups than did the FEV_1. Initial age-sex standardization was carried out using the nomograms referred to previously. However, it was observed that the variability about the mean FEF_{25-75} per cent predicted ($FEF_{25-75\%}$) was high (1 SD > 20%). Therefore, to decrease the variability of the $FEF_{25-75\%}$ and to increase the efficiency of the analysis, a score (FEF-Z score) was derived as follows: Children were divided into sex-specific, 5-yr age groups. Within each group, subjects were rank ordered, and the ranks were converted into a cumulative frequency distribution. Each rank was then assigned a score from a table of areas under a standard normal curve (16). The mean score within each group was thus 0 with a variance of 1. The scores can be interpreted as follows (figure 1): persons with a score of +1 had a $FEF_{25-75\%}$ equal to or greater than 84% of the members of their age- and sex-specific group; persons with a score of −1 had a $FEF_{25-75\%}$ equal to or greater than only 16% of their group. Linear regression (17) of the FEF-Z score on age failed to show any trend toward age-ordering of the ranks within each age- and sex-specific group for subjects 5 to 19 yr of age (all except 3 children were 19 yr of age or younger). Only children 5 to 9 yr of age were included in subsequent analyses.

A weighted mean FEF-Z score was obtained for the children in each household included in the analysis. The weights were derived from a random effects analysis of variance model (18), which had demonstrated a significant familial clustering of the FEF-Z score. The effect of the weighting procedure is to take into account the varying size of sibships in the calculation of the overall means (19).

When appropriate, comparisons were performed with the chi square test with a correction for continuity unless estimated cell size was less than 5, in which case Fisher's exact test was used. A step-down multiple linear regression model was used to assess the effect of a number of variables on the children's FEF-Z score (20).

Inclusion of subjects in analyses. The outcome of the overall sample selection used for this study has been presented in detail elsewhere (19).

Although respiratory symptom and illness questionnaires were completed for 650 children 5 to 9 yr of age, not all of these children had data available for smoking history and pulmonary function. Furthermore, because of the combination of subject refusal and the existence of single parent households, smoking data were not available for both parents in all households. To identify possible bias due to excluding subjects in the analyses, the comparability of various subject groups was assessed.

Personal smoking history data were available for only 67% of the study children. The percentage of nonrespondents to the questions about personal smoking was not significantly different for children with current persistent wheeze (28.3%, 17/60) from those without this symptom (33.9%, 193/569).

Smoking history data for both parents in the household were available for 51.7% (31/60) of children with current persistent wheeze, and 59.9% (341/569) of children without this symptom (p = NS). The availability of these data also was not significantly different for children with and without the symptoms of chronic cough and phlegm (52.4%, 11/21 versus 61.2%, 372/608).

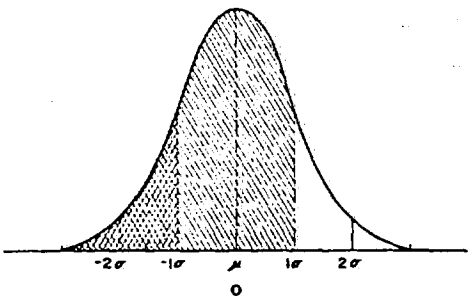

Fig. 1. Interpretation of the FEF-Z score. The FEF-Z scores are normally distributed with a mean (μ) of 0 and a variance (σ^2) of 1. Subjects with a score of 1 (1σ) would have an $FEF_{25-75\%}$ equal to or greater than 84% of their peers (*hatched and cross-hatched areas*). Subjects with a score of $-1(-1\sigma)$ would have an $FEF_{25-75\%}$ equal to or greater than only 16% of their peers (*cross-hatched area*) (19).

TABLE 1

AGE-SEX DISTRIBUTION OF THE INDEX CHILDREN AND THEIR SIBLINGS SURVEYED FOR RESPIRATORY ILLNESS SYMPTOMS IN EAST BOSTON, MASS., JANUARY–JUNE 1975

Age	Index Children		Siblings		Total in Each Age Group
	Male	Female	Male	Female*	
4	11	10	0	1	22
5	35	38	17	25	115
6	56	38	12	14	120
7	54	35	19	23	131
8	51	46	24	20	141
9	38	24	21	27	110
10	5	3	1	2	11
	250	194	94	112	650

* χ^2_1 for difference between males and females = 3.94; p = NS.

Forced expiratory volumes were performed satisfactorily by 60.8% (395/650) of the study children. Children with and without pulmonary function data were comparable with regard to sex distribution, average number of siblings per household, parent smoking history, type of home heating system, reporting of a doctor's diagnosis of asthma, and the reporting of current persistent wheeze. Children with missing data were significantly younger than those for whom function data were available, and they were significantly less likely to have ever smoked cigarettes.

Results

Six-hundred fifty children, 4 to 10 yr of age, from 414 families were interviewed. There were 444 index children and 206 of their siblings (table 1). The age distribution for the male and female chil-

TABLE 2

A HISTORY OF PAST OCCURRENCE OF RESPIRATORY ILLNESS AND SYMPTOMS IN CHILDREN 5 TO 9 YR OF AGE BASED ON QUESTIONNAIRES ADMINISTERED AT THE INITIAL INTERVIEW

Illnesses and Symptoms	Males Number (%)	Females Number (%)	Total (%)
Acute respiratory illness			
Croup	48 (14.0)	33 (10.8)	81 (12.5)
Bronchiolitis	3 (0.9)	2 (0.7)	5 (0.8)
Acute bronchitis	69 (20.1)	58 (19.0)	127 (19.5)
Pneumonia	44 (12.8)	41 (13.4)	85 (13.1)
Atopic illness			
Hay fever	7 (2.0)	5 (1.6)	12 (1.8)
Asthma	26 (7.6)	13 (4.2)	39 (6.0)
Eczema	26 (7.6)	21 (6.9)	47 (7.2)
Chronic respiratory symptoms			
Cough and phlegm	8 (2.3)	13 (4.2)	21 (3.2)
Wheeze			
No wheezing or occasionally with colds	301 (87.5)	268 (87.6)	569 (87.5)
Wheezing occasionally apart from colds*	9 (2.6)	7 (2.3)	16 (2.5)
Wheezing with colds and occasionally apart from colds on most days and nights	32 (9.3)	28 (9.2)	60 (9.2)
Missing data*	2 (0.6)	3 (1.0)	5 (0.8)
	n = 344	n = 306	n = 650

* These children with intermediate wheeze status and missing data were excluded from all subsequent analyses.

dren was not significantly different (χ^2_4 = 3.94, NS). The mean age for male children was 7.0 yr, and the mean age for female children was 6.9 yr.

Acute respiratory illnesses were reported to have occurred with equal frequency in male and female children (table 2). Episodes of acute bronchitis were the most frequently reported acute respiratory illness (19.5%), followed by episodes of pneumonia (13.1%), a history of croup (12.5%), and a history of bronchiolitis (0.8%).

Atopic diseases (except asthma) were also reported with equal frequency in male and female children (table 2). Eczema was the most frequently reported atopic disease (7.2%), followed by asthma (6.0%) and hay fever (1.8%).

Asthma was reported more frequently for male children (7.6%) than for female children (4.2%), although this difference was not significant. Current persistent wheeze occurred equally in both sexes (9.3% versus 9.2%). The reported symptoms of chronic cough and phlegm production were also not significantly different for male and female children (2.3% versus 4.2%). The 5 children with missing wheeze data (including 3 children with a doctor's diagnosis of asthma) and the 16 children in the intermediate wheeze group (wheezing occasionally apart from colds) were excluded from all subsequent analyses.

Of the children for whom a doctor's diagnosis of asthma was reported, 63.9% (23/36) had persistent wheezing compared with 6.2% (37/593) of children for whom a doctor's diagnosis of asthma was not reported (χ^2_1 = 124.12, $p < 0.001$). Similarly, children with a history of asthma were significantly more likely to report the presence of chronic cough and phlegm (13.9%, 5/36) than children without a history of asthma (2.7%, 16/593) ($p = 0.01$, Fisher's exact test). Among the nonasthmatic children with current persistent wheeze, 24.3% (9/37) reported the occurrence of chronic cough and phlegm compared with 1.3% (7/556) of the nonasthmatic children without persistent wheeze ($p < 0.001$, Fisher's exact test).

Children with current persistent wheeze had a significantly greater reported frequency of past episodes of acute bronchitis, pneumonia, and sinus trouble compared with children without current persistent wheeze (table 3). Moreover, children with persistent wheeze were significantly more likely to have been hospitalized in the past for a respiratory illness than children without current persistent wheeze (χ^2_1 = 31.52, $p < 0.001$).

Similarly, children with current persistent wheeze were more likely to report diseases considered to be atopic than children without this symptom (table 3). Asthma, hay fever, and eczema all were reported more frequently in the children with persistent wheeze.

Analysis of the prospective respiratory illness surveillance for the index children showed that 35% of all children experienced one or more lower respiratory illnesses in Year 1 and 22% of all children experienced such illnesses in Year 2 (table 4). Upper respiratory illnesses occurred in 36% of children in Year 1 and 21% of children in Year 2. Laryngotracheal illnesses were reported infrequently, 4% in Year 1 and 2% in Year 2.

For each year of the prospective surveillance, children for whom current persistent wheeze was reported at the initial interview experienced more lower respiratory illness than children without current persistent wheeze at the initial interview. The difference in the frequency of lower respiratory illness for children with and without current persistent wheeze was 15.6% for Year 1 and 21.9% for Year 2. In contrast, no significant dif-

TABLE 3

THE RELATION BETWEEN CURRENT PERSISTENT WHEEZE (PW) AND REPORTING OF RESPIRATORY ILLNESS AND ATOPIC DISEASE

	Children with PW (n = 60) (%)	Children without PW (n = 569) (%)	χ^2	p Value (%)
Acute bronchitis	19 (31.7)	102 (17.9)	5.74	0.017
Pneumonia	15 (25.0)	68 (11.9)	6.97	0.008
Sinus trouble	7 (11.7)	6 (1.1)	—	0.001*
Hospitalizations for respiratory illness	18† (30.0)	40 (7.0)	31.52	0.001
Asthma	23 (38.3)	13 (2.3)	—	0.001*
Hay Fever	4 (6.7)	6 (1.1)	—	0.02*
Eczema	5 (8.3)	40 (7.0)	—	NS*

* Fisher's exact test.

† For 13 of these 18 subjects, a doctor's diagnosis of asthma was reported.

TABLE 4

OCCURRENCE OF RESPIRATORY ILLNESS DURING A 2-YR PROSPECTIVE FOLLOW-UP OF THE INDEX CHILDREN—THE RELATIONSHIP TO CURRENT PERSISTENT WHEEZE

				Lower Respiratory Illness		Upper Respiratory Illness		Laryngotracheal Illness
		Total Number of Children		% of children with 1 or more episodes*		% of children with one or more episodes†		% of children with one or more episodes‡
Persistent Wheeze	yes	39		48.7		41.0		0.0
	no	350	Year 1	33.1	Year 1	35.7	Year 1	4.3
Total		389		34.7		36.2		3.9
Persistent Wheeze	yes	38		42.1		21.1		2.6
	no	342	Year 2	20.2	Year 2	21.3	Year 2	2.0
Total		380		22.4		21.3		2.1

* χ_1^2 for difference in number of lower respiratory illnesses for children with and without persistent wheeze: Year 1, $\chi_1^2 = 3.10$, $p < 0.10$; Year 2, $\chi_1^2 = 8.25$, $p = 0.004$.

† χ_1^2 for difference in number of upper respiratory illnesses for children with and without persistent wheeze: Year 1, $\chi_1^2 = 0.23$, NS; Year 2, $\chi_1^2 = 0.20$, NS.

‡ χ_1^2 for difference in number of laryngotracheal respiratory illnesses for children with and without persistent wheeze: Year 1, Fisher's exact test, NS; Year 2, Fisher's exact test, NS.

ference was found for upper respiratory illness, when the difference in frequency was 6% for Year 1 and 0.2% for Year 2.

Demographic factors, which might have been responsible for the difference in occurrence of lower respiratory illness in subjects with current persistent wheeze, were investigated. There were no significant differences between children with and those without persistent wheeze for the following variables: percentage of homes with gas heaters in the kitchen (33% versus 31%), reported history of prematurity (7% versus 7%), and density of persons per room (the mean for families of children with persistent wheeze was 1.0 person/room versus 0.99 person/room for families of children without persistent wheeze.

The relation between the reporting of current persistent wheeze and the children's own smoking history is presented in table 5. Eight of 43 children with current persistent wheeze (18.6%) reported that they had ever smoked cigarettes compared with 50 of 376 children (13.3%) who did not report this symptom (P = NS). In contrast, parental smoking habits were significantly related to the occurrence of current persistent wheeze (figure 2). Current persistent wheeze occurred in 1.85% (1/57) of children from households in which both parents never smoked cigarettes, in 6.85% (10/146) of children from households with 1 parent currently smoking, and in 11.8% (20/169) of children from households with 2 parents currently smoking (χ_1^2, trend = 6.36, p = 0.012). Chronic cough and phlegm were less closely related to parental smoking (figure 2), but followed a trend similar to that observed for current persistent wheeze. The percentages of children with chronic cough and phlegm were 1.7%, 2.7%, and 3.4%, respectively, for the 3 parent-smoking household groups (figure 2). When this analysis was repeated using those households in which

TABLE 5

THE RELATION BETWEEN CURRENT PERSISTENT WHEEZE* AND CHILDREN'S PERSONAL SMOKING HISTORY

	Persistent Wheeze		No Persistent Wheeze		Total	
	Number	(%)	Number	(%)	Number	(%)
Ever Smoked	8	(18.6)†	50	(13.3)	58	(13.8)
Never Smoked	35	(81.4)	326	(86.7)	361	(86.2)
Total	43	(100)	376	(100)	419	(100)

* 17/60 (28.3%) of children with current persistent wheeze and 193/569 (33.9%) of children without persistent wheeze did not answer the smoking questions.

† $\chi_1^2 = 0.521$ ($p > 0.30$) for the difference in the percentage of smoking children with and without current persistent wheeze.

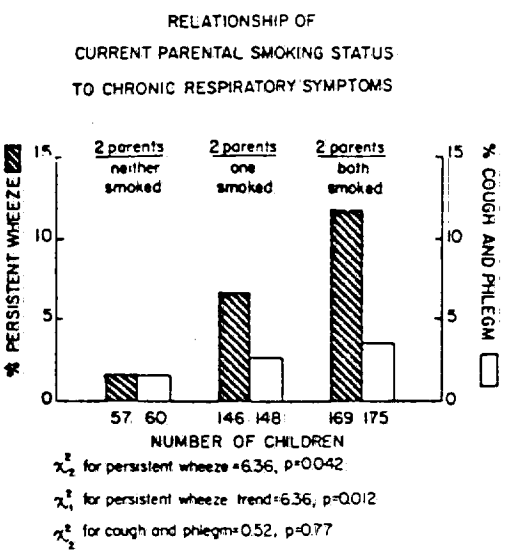

Fig. 2. Relation of current parental smoking status to chronic respiratory symptoms (persistent wheeze and cough and phlegm) in children. Both χ^2 values are the same since the total χ^2 was accounted for by the trend analysis.

mothers reported no symptoms of wheeze, the trend was the same. Children from households with 0, 1, or 2 smoking parents had prevalences of persistent wheeze of 0% (0/43), 1.8% (2/114), 7.7% (6/78), respectively (χ^2_1, trend = 6.109, p = 0.014). Analysis using households in which fathers did not wheeze gave prevalences of 0% (0/45), 5.7% (6/89), and 13.5% (10/74), respectively (χ^2_1, trend = 5.09, p = 0.025). Finally, analysis using households in which neither parent reported wheeze or chronic phlegm production gave prevalences of 0% (0/30), 3.6% (2/55), and 7.7% (2/26), respectively (χ^2_1, trend = 2.37, p > 0.2).

Children who reported current persistent wheeze had a significantly lower mean FEF-Z score than children without this symptom (−0.400 versus 0.060; table 6). After adjustment for the presence or absence of persistent wheeze, children with a present or past doctor's diagnosis of asthma had a lower mean FEF-Z score than children without such a diagnosis; however, the difference was not significant (table 6).

The relation of current persistent wheeze to the FEF-Z score also was examined by comparing the observed and expected prevalence of FEF-Z scores, which were 2 or more standard deviations below the population mean in children with and without this symptom. Three per cent (11/352) of the children without current persistent wheeze had scores 2 or more units below the mean, which is not significantly different from the 2.3% predicted from the areas under a standard normal curve (16). In contrast, 14.0% (6/43) of those children with current persistent wheeze had scores 2 or more units below the mean ($p < 0.01$ by the 1-sample binomial test).

Of the 395 children who performed satisfactory FVC maneuvers, data for the smoking habits of both parents were available for 238 (60.3%). Children from households in which both parents had never smoked cigarettes had a mean FEF-Z score of 0.473, or a 0.522 standard deviation greater than the mean score of −0.049 observed in children from households in which both parents were current smokers ($Z = 2.563$, $p = 0.005$ for the one-sided test for significance of difference; table 7). Children from households in which only 1 parent was a current cigarette smoker had a mean FEF-Z score that was 0.075, or a 0.398 standard deviation lower than that observed for children with 2 nonsmoking parents ($Z = 1.915$, $p = 0.028$ for the 1-sided test for significance of difference). The difference between the mean score for children from households with 1 and 2 currently smoking parents was not significant ($Z = 0.850$, $p = 0.198$, one-sided test for significance of difference). Analysis for linear trend revealed that the progressive decline in the mean FEF-Z score with increasing parental smoking was significant (Z_L, trend = 5.709, $p < 0.02$).

Current smoking status of the mother ($p = 0.017$) and the presence of current persistent wheeze ($p = 0.071$) were the most significant predictors of a child's FEF-Z score (table 8). A doctor's diagnosis of asthma, the child's personal smoking history, and current smoking status of the father were not significant predictors of FEF-

TABLE 6

THE FEF-Z SCORES FOR CHILDREN WITH OR WITHOUT CURRENT PERSISTENT WHEEZE BY DOCTOR'S DIAGNOSIS OF ASTHMA

	Mean FEF-Z Score	Number
Persistent wheeze	−0.400*	43
Asthma†	−0.618	15
No asthma	−0.283	28
No persistent wheeze	+0.060	352
Asthma	−0.217	4
No asthma	+0.065	348

For mean FEF-Z score, see methods.

* Normal deviate for comparison of mean FEF-Z score for children with and without current persistent wheeze = 2.85, p = 0.004.

† Normal deviate for weighted average difference of mean FEF-Z score between asthma and no asthma in the persistent wheeze and no persistent wheeze groups = 1.308, p = 0.192.

TABLE 7

THE RELATION OF PARENTAL CIGARETTE SMOKING TO MEAN FEF-Z SCORES IN CHILDREN 5 TO 9 YR OF AGE

	Two Parents Who Never Smoked	Two Parents, One of Whom is Current Smoker	Two Parents, Both of Whom are Current Smokers
Mean FEF-Z score	0.473*	0.075	−0.049†‡
Number of Children	33	94	111
Number of Siblings	26	67	78

* Normal deviate for the difference between mean FEF-Z score for the never smoking parent group and the 2 parent smoking group: Z = 2.563, p = 0.005, 1-sided test. Normal deviate for the difference between mean FEF-Z score for the never smoking parent group and the 1-parent smoking group; Z = 1.915, p = 0.028, 1-sided test.

† Normal deviate for the difference between mean FEF-Z score for 1-parent smoking and 2-parents smoking groups: Z = 0.850, p = 0.198.

‡ χ^2_1 for trend in mean FEF-Z score for parent smoking groups = 5.709, p = 0.01.

Z score. The total r^2 for the model was 0.08. An interaction variable (not shown in the table) for the mother's and father's current smoking also was not significant. Although lower respiratory illnesses were found to occur more frequently in children with persistent wheeze, this variable was not included in the regression model because of the relatively small number of persons with both persistent wheeze and such illnesses (table 4).

Discussion

The frequent reporting of current persistent wheeze observed in the present study was consistent with the finding of the Tuscon survey of a population of children and young teenagers (21). Our study also showed significant associations of persistent wheeze with a history of acute lower respiratory illness, history of atopic disease, and current parental cigarette smoking habits. Furthermore, this symptom was found to be associated with significantly lowered degrees of pulmonary function, as measured by $FEF_{25-75\%}$.

The excess frequency of respiratory illness in subjects with persistent wheeze confirmed several British studies (8, 22, 23), which demonstrated that children with current chronic respiratory symptoms report a higher frequency of past lower respiratory illness than those children without chronic symptoms. The prospective respiratory illness surveillance conducted in the present study demonstrated that children with current persistent wheeze experienced a higher frequency of lower respiratory illness episodes than those children without persistent wheeze. This finding made it unlikely that the relation between current persistent wheeze and the past history of lower respiratory illness noted previously was due solely to selective recall on the part of the parents of the children with current persistent wheeze.

Although children with current persistent wheeze

TABLE 8

LINEAR REGRESSION MODEL FOR CHILDREN'S FEF-Z SCORE

Variable	Regression Coefficient*	Standard Error of Regression Coefficient	F Ratio	p Value
Intercept	+0.231	—		
Mother a current smoker	−0.306	0.128	5.77	0.017
Current persistent wheeze	−0.412	0.227	3.28	0.071
Doctor diagnosis of asthma in child	−0.420	0.266	2.51	0.114
Child's smoking history	+0.028	0.019	2.13	0.146
Father a current smoker	−0.046	0.145	0.10	0.750
		Total r^2 = 0.08		

* All independent variables defined as Yes = 1, No = 0; total subjects in the analysis = 238.

reported a history of atopic diseases more frequently than nonwheezing children, the degree to which this wheezing syndrome represented true atopy or alternative mechanisms of abnormal airway reactivity was unknown, and could not be determined from this study. Burrows and associates (24) found "wheezy bronchitis" to be associated with the occurrence of hyperreactivity to a battery of 5 skin test antigens. However, in general population surveys, a history of wheeze usually has been found to far exceed the reporting of a history of hay fever or asthma (21, 24). Moreover, recent investigations of airway reactivity to irritants whose effects are not thought to be related to an atopic mechanism (e.g., irritant gases at low concentration (25, 26), cold air (27), and viral illness (28-30)) suggested that alternative, nonatopic mechanisms indeed may be involved in some wheezing syndromes.

Several other investigations have demonstrated that chronic respiratory symptoms in children, including the occurrence of wheeze, are reported more frequently in the children of parents who smoke cigarettes (31-38). Several of these studies have observed that the prevalence of wheeze in children was higher for those children whose parents also wheeze (31, 32, 39). However, the trend of increased wheezing with increasing parental smoking observed in our study children has been shown to be independent of parental history of wheezing, since a significant trend of similar magnitude persists when the analysis is restricted to nonwheezing parents of either sex. These data suggested, therefore, that exposure to parental cigarette smoke in our population is related to the occurrence of wheeze in children

All of the children included in the present report were included in a previous study that demonstrated an inverse relation between the degree of FEF_{75-75}, in children and the amount of parental smoking (19). Although we have restricted the present analysis to the youngest children in the overall study population, the effects of parental smoking on pulmonary function were similar in magnitude to those obtained when children 19 yr of age or younger were included in the analyses. This indicated that the effects of parental smoking could be measured early in life and were not, in fact, substantially dependent upon significant smoking by the children themselves.

Regression analysis was used to identify how factors such as parental smoking, children's own smoking, and the occurrence of wheeze affected the FEF-Z scores. Although the r^2 for the overall model was small (0.08), several interesting observations emerged from this analysis. Despite the fact that the presence of persistent wheeze was associated with lower FEF-Z scores (table 6), the mother's current smoking history was the most significant overall predictor of a lower FEF-Z score (table 8). This observation was consistent with an earlier study in this community (using a different sample of children) that also demonstrated that the mother's smoking history was a significant predictor of FEV_1, expressed as a per cent of predicted value (40). Similarly, Hasselblad and colleagues (41), in a study of 16,686 white children 6 to 14 yr of age, observed that, after age, height, and sex, the mother's current smoking (measured as packs per day) was the most significant predictor of the degree of FEV_1. Although these observations stress the importance of the most recent smoking experience of the mothers, the possibility also remained that smoking during gestation and the neonatal period may also have contributed to altered lung function. No satisfactory data are available concerning this early age group.

The failure to find that the father's smoking was a significant predictor of the degree of function in this and the other 2 studies cited would, at first glance, appear to contradict the observation of an inverse linear trend between the FEF-Z score and the number of parents smoking (19) (table 7). However, most of the effect in the trend analysis was between the households in which neither parent was a current smoker and households in which 1 parent was a current smoker. Differences between households where one and those where both parents smoked were less striking. Further analyses, particularly of the relation between rate of change of function with growth and parental smoking, are being undertaken to try to determine how these associations change with time.

The finding that the child's own smoking habits were not a significant predictor of the degree of function was in sharp contrast to previous work in this population in which these children were included (19). However, the prior analysis included children as old as 19 yr of age, whereas this analysis was restricted to those 5 to 10 yr of age. The number of smokers in this age group was quite small (table 5). Furthermore, those children who did report having smoked, smoked infrequently, usually less than 1 cigarette per week. Thus, for this age group, personal smoking did not occur often enough or with enough intensity to be a significant predictor of FEF-Z score.

The fact that the regression analysis identified the mother's smoking history as a stronger predictor of FEF-Z score than the symptom of persistent wheeze would suggest that the lower FEF-Z scores observed in the children of smoking parents was not simply a function of the fact that these children had a tendency to wheeze, and, therefore, would be more likely to experience episodes of subclinical bronchoconstriction at the time they were asked to perform the FVC maneuvers. The identification of persistent wheeze as the second strongest predictor of FEF-Z scores was open to several interpretations because of the cross-sectional nature of the data. Thus, it was equally likely that the presence of wheeze identified a group of children for whom wheeze was an additional marker for stable deficits in function and/or a group of children with transiently lowered degrees of function due to bronchomotor hyperreactivity.

A number of children had to be excluded from several of the analyses because of missing data. The possibility that these exclusions might have led to bias in the relation between persistent wheeze and the parental smoking and pulmonary function variables was explored. Children who were excluded were significantly younger and were significantly less likely to have ever smoked cigarettes than those included in the various analyses, but were not significantly different in their reported prevalence of current persistent wheeze. Furthermore, these excluded children were similar to those included in the analyses with regard to a number of demographic variables including the parental smoking histories, which might have influenced the reported relationships. Thus, it seems unlikely that differences between children included and not included in the analyses could explain the observations reported.

Existing data concerning the possible mechanisms by which passive exposure to cigarette smoke might lead to the occurrence of persistent wheezing are few, but a direct irritant and/or immunologic effect is possible (42). Similarly, lower respiratory illnesses might be influencing the occurrence of wheezing by either of these mechanisms (43).

The association of current persistent wheeze in children with a history of atopy, respiratory illness, and parental cigarette smoking to a lower degree of pulmonary function in children suggested that factors acting in childhood may be directly relevant to the subsequent risk of developing obstructive airway disease in adult life. The prospective test of this hypothesis remains the central goal of the study from which the present data have been derived.

Acknowledgment

The authors gratefully acknowledge the work of Kay Mooradian and Mary Folsom who collected the data, and Diane Straney who provided programming assistance.

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